(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 November 2001 (08.11.2001)

PCT

(10) International Publication Number
WO 01/82912 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/IB01/00715

(22) International Filing Date: 30 April 2001 (30.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2000 00704 28 April 2000 (28.04.2000) DK

(71) Applicant *(for all designated States except US)*: **P.N. GEROLYMATOS S.A.** [GR/GR]; 13 Asklipiou Street, GR-145 65 Kryoneri Attika (GR).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **XILINAS, Michel** [FR/CY]; 20-22 Leoforos Athinon, CY-6014 Larnaca (CY).

(74) Agents: **RASMUSSEN, Torben, Ravn** et al.; Internationalt Patent-Bureau, Høje Taastrup Boulevard 23, DK-2630 Taastrup (DK).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/82912 A2

(54) Title: TREATMENT OF PATHOLOGICAL CONDITIONS INFLUENCED BY THE ACTION OF MATRIX METALLOPROTEINASES (MMPs) USING PHANQUINONE

(57) Abstract: A use of phanquinone for the manufacture of a pharmaceutical composition for the prevention or the treatment of pathological conditions influenced by the action of matrix metalloproteinases (MMPs) is disclosed. Also methods of treatment or prevention of such conditions are disclosed.

TREATMENT OF PATHOLOGICAL CONDITIONS INFLUENCED BY THE ACTION OF MATRIX METALLOPROTEINASES (MMPs) USING PHANQUINONE

Introduction

The present invention relates to a new use of the known compound phanquinone. Especially, the invention pertain to the use of phanquinone for the manufacture of a pharmaceutical composition for treatment or prevention of pathological conditions influenced by the action of matrix metalloproteinase (MMP).

Background of the invention

A group of enzymes involved in the breakdown of various biological substances is generally known as matrix metalloproteinases, referred to herein as MMPs. The group of MMPs comprises at least 13 different enzymes, including stromelysin, gelatinase, and metalloelastinase.

The common characteristic of the enzymes of the MMP group is that they require and are dependent on the presence of Zn^{2+} to be active, as the structure of MMPs show the presence of a zinc(II) ionic site associated with the catalytic site.

The function of MMPs in the body is to degrade extracellular proteinious matrix components. MMPs degrade collagen, laminin, proteoglycans, fibronectin, elastin, gelatin, myelin etc. under physiological conditions. The normal action of MMPs is *inter alia* effective on tissue remodeling of articulation tissue, bone tissue and connective tissue. The homeostasis of the extracellular matrix is controlled by a delicate balance between the synthesis and activation of MMPs, the degradation of MMPs, and the presence of MMP inhibitors.

It is generally accepted that a derivation from the normal overall level of the MMPs and the proportion between the individual MMPs may play a role in pathological conditions involving tissue breakdown, e.g. rheumatoid arthritis; osteoarthritis; osteopenias such as osteoporosis, periodontitis, gingivitis, corneal epidermal or gastric ulceration; and tumour metastasis, invasion and growth. MMPs are also expected to be responsible, at least in part, for the development of neuroinflammatory disorders, including those involving myelin degradation, e.g. multiple sclerosis, as well as for the management of angiogenesis dependent diseases, which include arthritic conditions and solid tumour growth as well as psoriasis, proliferative retino-pathies, neovascular glaucoma, ocular tumours, angiofibromas and hemangiomas. However, the relative contribution of individual MMPs in any of the above disease states is not yet fully understood.

Modulation of MMP regulation is possible at several biochemical sites but direct inhibition of enzyme action provides a particularly attractive target to therapeutic intervention. *In vivo*, the MMPs are regulated by tissue inhibitors of metalloproteinases (TIMPs).

The present invention is directed to a synthetic compound having the property of inhibiting the action of MMPs. Thus, the compound is useful in the treatment or the prophylaxis of the above pathological conditions.

Prior Art

The involvement of inhibitors of MMPs in cancer has been the subject of continuous scientific interest for at least 10 years and investigations have pointed

not only to a role of inhibitors of MMPs in invasion and metastasis but also in tumour growth, apoptosis, transformation, and angiogenesis. The inhibitors of MMPs cannot only block tumor invasion and metastasis but also inhibit the growth of primary tumors. As an example, leukemia cells secrete in tissue culture MMPs, one of which is the known MMP-9. It has been shown that chemical chelators, such as EDTA and phenanthrolene, are able to inhibit the activity of said MMPs and halt the degradation of the matrix constituents (Dittman KH et al., Exp Hematol 23:155, 1995).

The balance between activation of MMPs and their inhibition is a crucial aspect of cancer invasion and metastasis. In colorectal, breast, prostate and bladder cancer, most patients with aggressive diseases have increased plasma levels of gelatinase B (Zucker S et al., Ann NY Acad Sci 878:212, 1999). The role of MMPs in tumour angiogenesis and growth is established in both human and animal experimental models wherein there is a necessity for the degradation of the stromal matrix during the neoplastic process and, either directly or indirectly, the tumour is able to achieve this via MMP action.

Both type I and type II diabetes complications (kidney, eye, peridontal) are likely to be improved by the administration of inhibitors of MMPs. Tetracycline analogues that inhibit MMPs have been evaluated experimentally (Ryan ME et al., Ann NY Acad Sci 878:311, 1999). Their results have shown a reduction in the incidence of cataract development, proteinuria and tooth loss. It is proposed that one of the mechanisms of action of inhibitors of MMPs in peridontal disease, irrelevant of diabetes complications, is the inhibition of elevated levels of

MMPs, including neutrophil and bone cell collagenases (MMP-8 and -13) which are associated with the host response in chronic adult periodontitis (Ashley RA et al., Ann NY Acad Sci 878:335, 1999).

It is known that articular cartilage is composed of an abundant extracellular matrix that is rich in collagen and sulfated proteoglycans. The contents of proteoglycans within the collagen network provide cartilage with compressibility and elasticity necessary to protect and cushion the subchondrial bone. During the development of osteoarthritis, the physical characteristics of the cartilage matrix become disrupted and a loss of collagen and proteoglycan from cartilage occurs, which is the hallmark of the disease (Leff RL Ann NY Acad Sci 878:201, 1999). In both osteoarthritis and rheumatoid arthritis as well as in other arthritis and fibrosis, the MMPs have been disclosed as implicated. A variety of cell types, including chondrocytes and synoviocytes, secretes the MMPs, and the progress of diseases is associated with an increase in the concentrations of MMPs in plasma and synovial fluid. Inhibition of the activity of such degenerative enzymes may halt or slow the progression of osteoarthritis and the other arthritis and fibrosis conditions and ameliorate the course of the diseases. In both human rheumatoid arthritis (Ahrens D et al., Arthritis Rheum 39: 1576, 1996) and in experimental animal uveitis (Di Girolamo N et al., Curr Eye Res 15:1060, 1996) there is an increased expression of MMPs (MMP-9, -1, and -3, respectively).

The generalised loss of bone, the development of osteoporosis, and the subsequent occurrence of fractures all increase with age. Oestrogens deficiency leads to an increase in bone resorption, probably

secondary to an increase in osteoblast number and collagenase activity. It has been shown (Williams S et al., Ann NY Acad Sci 878:191, 1999) that minocycline, a collagenase inhibitor, changes the spectrum of bone remodeling and throughout this activity favours bone formation.

Some members of the MMP family are active in vascular matrix remodeling in the pathogenesis of atherosclerosis. It seems that said MMPs may be over expressed in certain locations of atherosclerotic plaques and contribute to the destruction of connective tissue and thus plaque rupture. In the majority of lesion areas, however, matrix synthesis is likely to outstrip matrix degradation, because accumulation is a major feature of most atheromas. MMPs expressed in atherosclerosis are the matrix metalloproteinases-3 (stromelysin), -9, -12, and -13. This type of imbalance favouring matrix deposition is likely to be exacerbated in individuals with the 6A6A genotype in whom stromelysis expression is lower due to the weaker stromelysin promoter.

Acute coronary syndromes result from fissure, erosion or rupture of a vulnerable atherosclerotic plaque. The characteristics of a vulnerable plaque include a large lipid pool, an abundance of inflammatory cells and mediators, a reduced smooth muscle cell and collagen content and a thin overlying fibrous cap. There is evidence supporting that the plaque stabilisation may be achieved through inhibition of MMPs.

Matrix synthesis and degradation contribute to the morphological changes occurring after a myocardial infarction. Mast cells appear to play an important role in the destabilisation of the atherosclerotic plaque. Said instability is associated with increased

numbers of mast cells in culpit lesions. Activated mast cells secrete neutral proteases capable of degradation of the extracellular matrix by stimulating macrophages to produce MMP-9. It has been shown that administration of an inhibitor of MMPs attenuates early left ventricular models.

In the normal heart, cardiomyocytes are surrounded by extracellular matrix and latent MMPs produced primarily by cardiac fibroblasts. The development of congestive heart failure is associated with ventricular dilation and myocardial remodeling. It has been shown that the contributory mechanism for the initiation of the dilation remodeling is enhanced expression and potentially increased activity of left ventricular MMPs (Spinale FG et al., Circ Res 82:482, 1998). This may lead to activation of adverse MMPs remodeling, cardiac dilatation and cardiac failure.

Changes in copper concentration in the arterial wall are important because of cross-linkage formation in collagen and elastin. In a study undertaken to evaluate the concentrations of heavy metals in arterial wall, serum and calcified atherosclerotic plaques showed an accumulation of Ca, Mg, Zn and Cu atherosclerotic plaques (Iskra M et al., J Trace Elem Med Biol 11:248, 1997).

It has been shown that EDTA, 1,10-phenanthroline as well as inhibitors of MMPs reduce the activities of MMPs that dysregulate extracellular matrix and contribute to vascular remodeling as complications of atherosclerotic lesions (Galis ZS et al, J Clin Invest 94:2493, 1994).

The abdominal aortic aneurysms represent a chronic degenerative condition associated with a life-threatening risk of rupture. The condition is thought to be due to a progressive degeneration of the aortic

wall elastin and collagen and in the increased production locally of MMPs. It has been shown that even short term treatment experimentally with inhibitors of MMPs suppress the expression of MPPs in the aortic tissue.

Phanquinone (4,7-phenanthroline-5,6-dione) has hitherto been used for the treatment of various disorders, such as amoebiasis. Phanquinone has been sold by CIBA-GEIGY under the trademark ENTOBEX. However, at present, the marketing of phanquinone has been stopped.

Phanquinone has received renewed interest in recent years and has been suggested for the treatment of Alzheimer's disease in WO 99/09981.

Disclosure of the invention

According to the present invention the new use of phanquinone for the manufacture of a pharmaceutical composition for the treatment or prevention of pathological conditions influenced by the action of MMP is provided.

Various diseases are influenced by MMPs. Examples of such diseases are tumor metastasis and neo-angiogenesis, including breast, colorectal, prostate, pancreatic cancer and leukemia; rheumatoid arthritis, osteoporosis and osteoarthritis; corneal ulceration; multiple sclerosis; diabetic complications, including periodontal disease; and atherosclerosis, including heart failure, myocardial infarction, and ischaemic heart disease. The common feature for the pathological conditions which may be influenced by MMPs is that such conditions involve tissue breakdown. In general, the cause of the disease influenced by MMPs is due to an over-activity of MMPs leading to increases degradation of tissue. However, in certain kinds of

diseases, such as atherosclerosis, the lack of sufficient MMP activity may provide for growth of undesired tissues, such as atheromas.

The dosage of phanquinone optimal *in vivo* for treatment or prevention of the pathological condition influenced by MMPs may be determined by a physician upon conducting routine experiments. An example of such an experiment is to monitor the inhibiting effect of phanquinone in an extracellular body fluid in contact with the tissue affected by the pathological condition. Beginning with relatively low doses (5-10 mg/day), a physician may monitor the inhibition of the MMPs in the body fluid. If there is no or only an insubstantial increase in the inhibition of the MMPs, the dosage may be raised until such a desired inhibition is observed. Another example is monitoring the clinical signs and symptoms of the pathological condition by using clinical measurements.

The amount of phanquinone administered to a subject in need thereof must be sufficient to treat or prevent the pathological condition influenced by the action of MMPs. In on aspect of the invention, the daily administered amount of phanquinone is 1 mg to 1 g. E.g., the phanquinone is administered in an amount of 5 mg to 100 mg one to three times daily. However, it may be desired to administrate phanquinone for some indications in amounts in excess of 1 g per day. According to another aspect of the invention, phanquinone is administered in an amount of 1 g to 10 g per day.

As phanquinone is a chelator which scavenge heavy metals, it may be desired to administrate a metal salt or prosthetic group prior to, concurrent with or subsequent to the administration of phanquinone to avoid deficiency of said metal salt or prosthetic

group. The amount of the metal salt or prosthetic group is suitably sufficient for impeding any detrimental side effect of phanquinone administration. A suitable daily amount is 5 µg to 2 mg, preferably 0.5 mg to 1 mg. It may be desired, in a first period to administrate phanquinone and in a second period the metal salt or prosthetic group. As an example, the first period may be one to three weeks and the second period one to four weeks.

It may be desired to administrate a further inhibitor of MMPs besides phanquinone. In a preferred embodiment of the invention, one or more further inhibitors of MMPs different from phanquinone is administered prior to, concurrent with or subsequent to the administrating of phanquinone, said further inhibitors having another activity toward the individual MMPs. The advantage of co-administration of one or more further inhibitors of MMPs is due to the fact that the MMP group consists of at least 13 different enzymes responding differently to a specific inhibitor. Administration of a further inhibitor besides phanquinone may allow for a targeted treatment of a certain pathological condition. Various inhibitors of MMPs are disclosed in the prior art and may be selected by the person skilled in the art according to the need thereof. The amount of the further inhibitor is preferably sufficient for increasing the effect of the prevention or treatment of the pathological condition influenced by the action of MMP. A suitable daily amount of the further inhibitor may be 1 mg to 1 g, preferably 5 mg to 250 mg.

The pharmaceutical composition manufactured using phanquinone may be formulated in any galenic formulation enabling phanquinone to enter the body.

Generally, suitable formulations include pharmaceutical compositions formulated for oral, parenteral or intradermal administration.

Parenteral formulations include intravenous and intra coronary infusion and injection liquids. Parenteral formulations are generally preferred when high dosages are to be administered and in the treatment of acute disease states.

It may be desirable to formulate the pharmaceutical composition as a single pharmaceutical composition in cases wherein the pharmaceutical composition comprise more than one active component. Furthermore, including the active ingredients in a single pharmaceutical composition decreases the possibility of maltreatment of the subject. However, it may be advantageous to formulate the pharmaceutical composition as two or more separate pharmaceutical entities for sequential or substantially simultaneous administration.

In one aspect of the invention a method is provided for the treatment of a subject having or suspected of having a pathological condition influenced by the action of MMP, comprising administering to the subject an amount of phanquinone effective to treat or prevent the pathological condition.

In another aspect of the invention a method is provided for treating a subject having or suspected of having a pathological condition influenced by the action of MMP, comprising administering to the subject an amount of phanquinone effective to inhibit the action of MMP.

In a further aspect of the invention a method is provided for treating a subject having or suspected of having a pathological condition influenced by the

action of matrix metalloproteinase (MMP), comprising administering to said subject:

(a) an amount of phanquinone effective to treat or prevent the pathological condition influenced by the action of MMP, and

(b) an amount of a compound or a mixture of compounds selected from the group comprising metal salts, prosthetic groups and inhibitors of MMPs different from phanquinone having another activity towards the individual MMPs.

Detailed description of the invention

In the following the invention will be explained in further detail. The proposed mechanism of action of the invention is not intended to limit the invention to said mechanism.

At present, the applicant believes that phanquinone and matrix metalloproteinases by competition chelate zinc from a common pool. Phanquinone has the ability to penetrate tissues, biological fluids, cells and pathological formations like atheromas, metastatic cells, degenerative cells, neo angiogenesis cells and inflammatory tissue. When phanquinone has entered the biological area involved in the pathological condition, the zinc(II) ion is captured from the free pool existing due to the equilibrium between MMPs containing zinc and MMPs lacking zinc. Phanquinone having chelated a zinc(II) ion then moves away from the area involved in the pathological condition and into the interstitial fluid, the lymph, the blood, the urine or the bile and is cleared from the body. The deprivation of zinc from the direct environment of the zinc requiring matrix metalloproteinases inhibits the action of the MMPs.

The pharmaceutical composition manufactured using phanquinone preferably comprises one or more pharmaceutical acceptable carriers and, optionally, one or more further active constituent(s). The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof. In a preferred embodiment, the phanquinone and, optionally, further active constituents in the pharmaceutical composition are purified.

It will be appreciated that the amount of phanquinone and, optionally, further active constituents required for said treatment or prevention will vary according to the route of administration, the disorder to be treated, the condition, age, the file history of the subject, and the galenic formulation of the pharmaceutical composition, etc. When treating a patient diagnosed as having a pathological condition influenced by the action of MMPs, the amount of phanquinone is preferably effective to provide for at least a partially inhibition of at least one of the enzymes belonging to the group of MMPs.

In on aspect of the invention, a suitable therapeutically effective amount of phanquinone in the pharmaceutical composition is, for example, 1 mg to 1 g, preferably 5 mg to 100 mg. In another aspect of the invention, up to 10 g of phanquinone may be formulated in a single pharmaceutical composition. If further inhibitors of MMPs are included in the pharmaceutical composition, the amount of phanquinone is preferably effective to the treatment or prevention of the pathological disorder influenced by the action of MMPs. The amounts of further inhibitors of MMPs in the pharmaceutical composition are in one aspect 5 mg to

250 mg, more preferred 10 mg to 50 mg and 5µ to 2 mg. In another aspect of the invention, the amount of further inhibitors of MMPs may be up to 10 g.

The actually administered amounts of phanquinone and, optionally, further active constituents may be decided by a supervising physician. If the pharmaceutical composition in addition to phanquinone comprises further active constituents they may be in the same composition for administering in combination concurrently, or in different compositions for administering substantially simultaneously but separately, or sequentially. If the active constituents are administered sequentially, the further active ingredients may be administered prior or subsequently to the administering of phanquinone.

Pharmaceutical formulations include those suitable for parenteral (including intramuscular, intracoronary, intra-articular and intravenous), oral, rectal or intradermal administration. Oral administration is the preferred route in one aspect of the invention, while the parenteral route is preferred in another aspect of the invention. Thus, the pharmaceutical composition may be formulated as tablets, pills, syrups, capsules, suppositories, solutions or emulsions for parenteral injection of infusion, formulations for transdermal application, powders, especially lyophilized powders for reconstitution with a carrier for intravenous administration, etc. The pharmaceutical compositions may be prepared using conventional carriers.

The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapy is administered. The carriers in the pharmaceutical composition may comprise a binder, such as microcrystalline cellulose, carboxymethylcellulose,

polyvinylpyrrolidone (polyvidone or povidone), gum tragacanth, gelatine, starch, lactose or lactose monohydrate; a disintegrating agent, such as alginic acid, maize starch and the like; a lubricant or surfactant, such as magnesium stearate, or sodium lauryl sulphate; a glidant, such as colloidal silicon dioxide; a sweetening agent, such as sucrose or saccharin; and/or a flavouring agent, such as peppermint, methyl salicylate, or orange flavouring.

Pharmaceutical formulations suitable for oral administration, e.g. tablets and pills, may be obtained by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by mixing the constituent(s), and compressing the mixture obtained in a suitable apparatus into tablets having a suitable size. Prior to the mixing, the phanquinone may be mixed with a binder, a lubricant, an inert diluent and/or a disintegrating agent and the further optionally present constituents may be mixed with a diluent, a lubricant and/or a surfactant.

In a preferred embodiment, free-flowing phanquinone powder is mixed with a binder, such as microcrystalline cellulose, and a surfactant, such as sodium lauryl sulphate, until a homogeneous mixture is obtained. Subsequently, another binder, such as polyvidone, is transferred to the mixture under stirring. When a uniform distribution is obtained, the mixture is passed through granulating sieves and dried by desiccation before being compressed into tablets in a standard compressing apparatus.

In a second preferred embodiment, free-flowing phanquinone powder is mixed with surfactants and/or emulsifying agents, such as Sapamine® (N-(4'-stearoyl amino phenyl)-trimethylammonium methyl sulphuric acid)

and lactose monohydrate until a uniform distribution of the constituents is obtained. A second preparation containing a disintegrating agent, such as maize starch, is added to the phanquinone mixture while being continuously stirred. Such a second preparation may be prepared by adding excess boiling water to a maize starch suspended in cold water. The final mixture is granulated and dried as above and mixed with maize starch and magnesium stearate and finally compressed into tablets in a standard apparatus.

A tablet may be coated or uncoated. An uncoated tablet may be scored. A coated tablet may be coated with sugar, shellac, film or other enteric coating agents.

Pharmaceutical formulations suitable for parenteral administration include sterile solutions or suspensions of the active constituents. An aqueous or oily carrier may be used. Such pharmaceutical carriers may be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Aqueous parenteral solutions for intravenous or intra-articular injection or infusion may be prepared by dilution to the desired concentration with an aqueous solvent or emulsifying agent, like water containing dissolved carboxymethylcellulose or polysorbate, such as polysorbate 80, ethyl oleate, Tween 20, or the like. Prior to the dissolution, phanquinone may initially be pre-dissolved in an organic solvent, preferably an aprotic solvent like DMSO, DMF, and the like.

Formulations for parenteral administration also include a lyophilized powder comprising phanquinone and, optionally, further active constituents that is

to be reconstituted by dissolving in a pharmaceutically acceptable carrier that dissolves the active constituents, e.g. an aqueous solution of carboxymethylcellulose and lauryl sulphate. Parenteral formulations are preferably made isotonic by adjusting with suitable electolytes.

When the pharmaceutical composition is a capsule, it may contain a liquid carrier, such as a fatty oil, e.g. cacao butter.

Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The compositions may be solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition may be formulated as a suppository, with traditional binders and carriers such as triglycerides.

In yet another embodiment, the phanquinone may be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra;* Sefton, CRC Crit. Ref. Biomed. Eng. 14: 201 (1987); Buchwald et al., Surgery 88: 507 (1980); Saudek et al., N. Engl. J. Med. 321: 574 (1989)). In another embodiment, polymeric materials may be used (cf. Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J. Macromol. Sci. Rev. Macromol. Chem. 23: 61 (1983); see also Levy et al., Science 228: 190 (1985); During et al., Ann. neurol. 25: 351 (1989); Howard et al., J. Neurosurg. 71: 105

(1989)). In yet another embodiment, a controlled release system may be placed in proximity of the therapeutic target, thus requiring only a fraction of the systemic dose (cf. e.g., Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)).

Other controlled release systems are discussed in the review by Langer (Science 249: 1527-1533 (1990)).

In one embodiment of the pharmaceutical composition, phanquinone and the, optionally, further active constituents, are comprised as separate pharmaceutical entities. By way of example, one entity may comprise phanquinone and another entity may comprise a metal salt or prosthetic group. The two entities, may be administered simultaneously or sequentially. For example, the entity comprising phanquinone can be administered, followed by administration of the second entity within a day, week, or month of phanquinone administration. If the two entities are administered sequentially, the entity comprising phanquinone is preferably administered for one to three weeks followed by a wash out period of one to four weeks, during which the entity comprising a metal salt or prosthetic group is administered but not the entity comprising phanquinone. After the wash out period, the treatment may be repeated.

The pharmaceutical composition may be provided as a pack or kit comprising one or more entities containing one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally, associated with such entities may be a notice in the form described by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice

reflects approval by the agency of manufacture, use or sale for human administration.

The various different diseases influenced by the action of MMPs which may be treated according to the present invention can be administered phanquinone and optionally further pharmaceutical active compounds in accordance with suitable dosage forms and regimes. As an example, neoplasias and in particular neo-angiogenesis, metastasis and apoptosis of tumors, and neoplastic diseases in general, may be treated by infusing 0.25 g to 4 g phanquinone, preferably about 0.5 g, dissolved or emulsified in a suitable amount of carrier, such as 100 ml to 1000ml, preferably around 250 ml for 1 to 4 weeks. The treatment may be repeated after 1 to 4 months if considered suitable by the attending physician. For solid tumors and advanced states of neoplasias the amount of phanquinone administered is generally in the higher end of the above range, that is between 0.5 and 4 g. Between treatments with phanquinone by infusion, phanquinone may be administered orally, e.g. by administering 50 mg to 500 mg one to three times daily.

Another example is the treatment of rheumatic diseases, such as osteo-arthritis, rheumatoid arthritis, and autoimmune diseases. Suitably, these diseases may be treated by intra-articular injection or infusion of 250 to 500 mg phanquinone dissolved in an appropriate amount and kind of carrier in a time period of 4 to 14 days. Alternatively, the same dosage regime as described for neoplasias may be used.

Yet another example is the treatment of acute coronary syndromes, such as unstable angina, refractory unstable angina and acute myocardial infarct. Acute coronary syndromes may be treated by administering 250 mg to 4 g phanquinone dissolved in

an appropriate amount and kind of solvent. Suitably, the mode of administration can be intra-coronary or intravenous infusion during the acute phase of the disease. For refractory unstable angina or for large infarcts or for highly thrombogenic coronary arteries, the amount of phanquinone is usually in the higher end of the above range, i.e. between 1 g and 4 g. Optionally, the acute phase treatment can be followed by orally administration of phanquinone in an amount of 50 mg to 500 mg, preferably about 100 mg, one to three times daily for 1 to 8 weeks.

Other features and advantages of the invention will be apparent from the following examples, which, in conjunction with the accompanying drawings, illustrate by way of example the principles of the invention.

Examples

EXAMPLE 1

Preparation of a pharmaceutical composition comprising phanquinone

250 g of phanquinone were mixed with 200 g sapamine® (N-(4'-stearoyl amino-phenyl)-trimethylammonium methyl sulphuric acid) and 1025 g lactose mono-hydrate for a period of 5 minutes. 300 g of boiling water was added in one go to a mixture of 100 g maize starch in 100 g cold water. The maize suspension, cooled to 40°C, was added to the phanquinone-containing powder mixture under continuous stirring. The mixture was granulated using a 2.5 mm sieve and desiccated for 18 hours at 40°C. The dry granules were mixed with 400 g maize starch and 20 g magnesium stearate. The final mixture was formulated

into tablets having a diameter of 8.0 mm and a weight of 200 mg.

Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

It will be obvious to a person skilled in the art that the invention thus described may be varied in many ways. Such variation are not to be regarded as a departure from the spirit and scope of the invention, and all such modifications, as would be obvious to a person skilled in the art, are intended to be included in the scope of the following claims.

C L A I M S

1. A use of phanquinone for the manufacture of a pharmaceutical composition for treatment or prevention of pathological conditions influenced by the action of matrix metalloproteinase (MMP).

2. The use according to claim 1, wherein the disease influenced by the action of matrix metalloproteinase is tumor metastasis and neo-angiogenesis, including breast, colorectal, prostate, pancreatic cancer and leukemia; rheumatoid arthritis, osteoporosis and osteoarthritis; corneal ulceration; multiple sclerosis; diabetic complications, including periodontal disease; and atherosclerosis, including heart failure, myocardial infarction, and ischaemic heart disease.

3. The use according to claim 1 to 2, wherein phanquinone is administered in a daily amount of 1 mg to 1 g.

4. The use according to claim 1 or 2, wherein phanquinone is administered in a daily amount of 1 g to 5 g.

5. The use according to any of the preceding claims, wherein a metal salt or prosthetic group is administered prior to, concurrent with, or subsequent to the administering of phanquinone.

6. The use according to claim 5, wherein the amount of a metal salt or prosthetic group is effective to inhibit a detrimental side effect of phanquinone administration.

7. The use according to any of the preceding claims, wherein an inhibitor of MMPs different from phanquinone and having another activity towards the individual MMPs is administered prior to, concurrent with or subsequent to the administering of phanquinone.

8. The use according to any of the preceding claims, wherein the pharmaceutical composition is formulated for oral, parenteral or intradermal administration.

9. The use according to any of the claims 1 to 8, wherein the pharmaceutical composition is formulated as a single pharmaceutical composition.

10. The use according to any of the claims 5 to 9, wherein the pharmaceutical composition is formulated as two or more separate pharmaceutical entities for sequential or substantially simultaneous administration.

11. A method of treating a subject having or suspected of having a pathological condition influenced by the action of matrix metalloproteinase (MMP), comprising administering to the subject an amount of phanquinone effective to treat or prevent the pathological condition.

12. The method according to claim 11, wherein the disease influenced by the action of matrix metalloproteinase is tumor metastasis and neo-angiogenesis, including breast, colorectal, prostate, pancreatic cancer and leukemia; rheumatoid arthritis, osteoporosis and osteoarthritis; corneal ulceration; multiple sclerosis; diabetic complications, including periodontal disease; and atherosclerosis, including heart failure, myocardial infarction, and ischaemic heart disease.

13. A method of treating a subject having or suspected of having a pathological condition influenced by the action of matrix metalloproteinase (MMP), comprising administering to the subject an amount of phanquinone effective to inhibit the action of MMP.

14. A method of treating a subject having or suspected of having a pathological condition influenced by the action of matrix metalloproteinase (MMP), comprising administering to said subject:

(a) an amount of phanquinone effective to treat or prevent the pathological condition influenced by the action of MMP, and

(b) an amount of a compound or a mixture of compounds selected from the group comprising metal salts or prosthetic groups and inhibitors of MMPs different from phanquinone having another activity towards the individual MMPs.

15. The method according to claim 14, wherein the total amount of the compound(s) in (b) is sufficient for increasing the effect of the prevention or treatment of a pathological condition influenced by the action of MMP or for impeding any detrimental side effect.

16. The method according to claim 11, 13, or 14, wherein the daily administered amount of phanquinone is 1 mg to 1 g.

17. The method according to claim 11, 13, or 14, wherein the daily administered amount of phanquinone is 1 g to 5 g.

18. The method according to claim 14, wherein the amount of the compound(s) in (b) is 5 µg to 250 mg.

19. The method according to claim 14, wherein (a) phanquinone and (b) the compound(s) are comprised in a single pharmaceutical composition.

20. The method according to claim 14, wherein (a) phanquinone and (b) the compound(s) are administered substantially simultaneously.

21. The method according to claim 14, wherein (a) phanquinone and (b) the compound(s) are administered sequentially.

22. The method according to claim 21, wherein (a) phanquinone is administered in a first period followed by a second period, wherein (b) the compound(s) are administered.

23. The method according to claim 22, wherein the first period is one to three weeks and the second period is one to four weeks.

24. The method according to any of the claims 18 to 36, wherein the subject is human.

25. The method according to claim 11 or 14, wherein phanquinone is formulated for oral administration.

26. The method according to claim 11 or 14, wherein phanquinone is formulated for parenteral administration.

27. The method according to claim 11 or 14, wherein phanquinone is formulated for intradermal administration.